REMARKS

Amendments to the claims are supported by the original description. The nucleotide analog limitation of Claim 54 (*i.e.*, specifies a probe particularly adapted for interaction with RNA targets) has been incorporated into independent Claim 44, and Claim 54 has been cancelled. This clarifies that the claimed device is particularly adapted for amplifying and detecting RNA targets which are not synthesized as primer extension products. New Claim 55 finds support in the Specification and Drawings. Figures 5A-5B show results obtained using immobilized molecular beacon hybridization probes in an array format, and a set of solution-phase primers that were not immobilized to the solid support (see the description of procedures under Example 9). In this arrangement, RNA amplification products were synthesized in solution and then detected on the array following hybridization to the immobilized probes. Amplicons produced in the transcription-based amplification reaction must have been synthesized free in solution, since primers had not been immobilized to the solid support. Immobilizing a promoter-containing primer to the solid support comprising an immobilized probe (*e.g.*, results obtained using such a device being illustrated in Figures 5C-5D) would not change the fact that RNA amplicons enter the solution-phase, because transcription-based amplification reactions, such as TMA reactions, synthesize transcripts using an RNA polymerase that initiates transcription following promoter recognition, and not by extension of primers, regardless of their immobilization status. The new claim also is supported by the disclosure appearing on page 13 at lines 11-14, which discusses that the solid support can be a bead; and by the disclosure appearing on page 16 at lines 9-17, which discusses alternative array formats. No new matter has been introduced by these amendments.

Claims 44-52 and 55 will be pending following entry of this Response.

Entry of this Response is respectfully requested.

The Rejections Under § 103(a)

The nucleotide analog limitation of rejected Claim 54, now cancelled, has been incorporated into Claim 44. Accordingly, Applicant's response to the rejection of cancelled Claim 54 is now relevant to all pending claims. Claims 44-48 and 50-52 are addressed separately from Claim 49.

I. The Rejection of Claims 44-48 and 50-52 Under § 103(a)

Proposed Modification Renders Prior Art Unsatisfactory for Intended Purpose; and
Proposed Modification Inappropriately Changes the Principal of Operation of Prior Art

Cancelled Claim 54, now corresponding to amended Claim 44, has been rejected under 35 U.S.C. § 103(a) over the combined disclosure contained in U.S. Patent No. 6,060,288 ("**Adams**" hereafter), U.S. Patent No. 6,310,354 ("**Hanninen**" hereafter), *Histochem. Cell Biol.* **108**:431-437 (1997) ("**Mueller**" hereafter), and *Nucl. Acids Res.* 26:2224-2229 (1998) ("**Majlessi**" hereafter). The reasoned logic of the rejection has been made of record, but essentially alleges the obviousness of modifying the construct of **Adams** to create a device for synthesizing freely diffusible RNA amplicons, and then detecting those amplicons using an immobilized probe that is labeled prior to contact with a DNA polymerase. Applicant respectfully traverses the rejection for the following reasons.

Amended Claim 44, together with Claims 45-48 and 50-52 cannot be considered obvious under § 103(a) by the reasoning in the Office Action for at least two reasons: (1) the suggested modification would inappropriately render the prior art unsatisfactory for its intended purpose; and (2) the suggested modification would inappropriately require a change in the principle under which the prior art inventions were designed to operate (*see* M.P.E.P. § 2143.01). **Adams**, in the Background section addresses the high rate of sample-to-sample contamination known to plague PCR procedures, and presents solutions which universally involve synthesis of amplification products that are permanently

attached to a solid support. Critical to the solution offered by **Adams** is the retention of amplification products on the solid support, and avoidance of amplicons that can diffuse or cross-contaminate other samples. **Hanninen** discloses, "the *crucial point* of [the] invention is the use of two-photon excited fluorescent signal to detect the formation of nucleic acid amplification products," and measurement of fluorescent emissions from single microparticles when they randomly float through the restricted focal volume of a two-photon exciting laser beam (*see* col. 5 at lines 42-48; emphasis added). **Hanninen** teaches a method whereby fluorescent label indicative of a particular target nucleic acid is concentrated onto the surface of a microparticle (*e.g.*, by capturing labeled primer extension products using an immobilized unlabeled capture probe), and the concentrated label detected while substantially ignoring free label in solution (*e.g., see* col. 2 at lines 65-67; col. 3 at lines 4-6; and col. 3 at lines 53-57). Disposing labeled probe onto the microparticles of **Adams** in view of **Hanninen** prior to contact with a nucleotide polymerizing enzyme (*i.e.*, as required by the instant claim language) would defeat the purpose of gathering label for detecting amplicon while reducing background, and so would change the principle of operation of the detection system taught by **Hanninen**. **Mueller** illustrates in Figure 1 the use of paired sets of primers in the 3SR isothermal amplification procedure, where each primer comprises a T7 promoter. The promoter serves as a recognition sequence for T7 RNA polymerase which transcribes sense and anti-sense RNA copies of a downstream DNA sequence in the 3SR reaction. Substituting and using the 3SR reagents of **Mueller** in the device of **Adams** and **Hanninen** would have resulted in a system for creating RNA amplicons free in solution. As pointed out by the Examiner, **Majlessi** teaches that 2'-methoxy oligonucleotide probes are particularly advantageous when used for detecting RNA targets (*see* Office Action at the top of page 8, citing **Majlessi** at page 2229). Because RNA amplicons to be synthesized and captured by the suggested obvious device would be free in solution, and not tethered to a solid support, there are conflicts between the suggested obvious device and the objective and principle of operation underlying the device disclosed by the **Adams** primary reference. In other words, the obviousness-type rejection requires modifying the prior art in a manner that renders it unsatisfactory for the intended use of producing permanently tethered

amplicons in accordance with the primary reference, and substantially changes the principle of operation of both the primary and secondary references.

M.P.E.P. § 2143.01 provides guidance concerning the basic requirements of a *prima facie* case of obviousness, and is relevant to the present case. First, this section specifies that, "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *In re Gordon*, 733 F.2d 900,221 USPQ 1125 (Fed. Cir. 1984). Second, the same section specifies, "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). The principle of operation of the device and method taught by **Adams** involves synthesizing amplification products that are permanently immobilized to a solid support – purposely avoiding production of amplicons free in solution. Immobilizing and using promoter-primers in accordance with the suggested obvious device of **Adams, Hanninen** and **Mueller** would result in a device configured for production of free RNA amplicons, and so would go directly counter to the teaching of **Adams**. Detection of RNA amplicons using an immobilized unlabeled capture probe in accordance with **Hanninen**, who never suggests immobilizing labeled probe to microparticles prior to contact with a DNA polymerase, cannot undo the fact that amplicons produced in accordance with the suggested intended use of the device are the sort **Adams** seeks to avoid (*i.e.*, amplicons free in solution). Finally, the amendment of Claim 44 to incorporate the 2'-methoxy probe limitation of cancelled Claim 54 clarifies that the claimed device is configured for synthesizing and detecting RNA amplicons, something actually confirmed by the teaching of **Majlessi** which is cited as prior art. Because the suggested obvious device would give rise to RNA amplicons free in solution, and because those RNA amplicons would not be permanently joined to a solid support as a means for reducing carryover contamination, the suggested modification would render the prior art unsatisfactory for its intended purpose. Additionally, because the principle of

operation underlying the prior art invention being modified must be fundamentally changed to result in the suggested obvious device, the case for *prima facie* obviousness has not been made and should not be maintained. For these reasons, withdrawal of the § 103 rejection of Claims 44-48 and 50-52 is respectfully requested.

Aggregated Disclosure of Cited Prior Art Does Not Teach All Elements of Claimed Invention

Yet another reason favoring patentability of the claims relates to deficiencies in the disclosure of the cited prior art. The rejection mistakenly characterizes **Adams** as teaching a device comprising an immobilized hybridization probe that is labeled prior to contact with a nucleotide polymerizing enzyme. The Action states in the middle of page 3, "[t]herefore, since the probe is hybridized to an immobilized amplicon, the probe is itself immobilized, according to Applicant's definition." The error here is that the immobilized amplicons referenced in the rejection do not even exist until after the disclosed device has been contacted with a nucleotide polymerizing enzyme (*e.g.*, a DNA polymerase) which mediates amplicon synthesis. Thus, the immobilized labeled hybridization probe element of the claimed invention is not taught by **Adams**. Page 4 of the Action refers to **Hanninen** teaching "immobilized labeled fluorescent probes." However, none of the cited passages in the **Hanninen** patent support a showing of a labeled hybridization probe being immobilized prior to contact of the disclosed device with a nucleotide polymerizing enzyme (*e.g.*, a DNA polymerase). In fact, when **Hanninen** describes probe immobilized to a microparticle prior to conducting an amplification reaction (*i.e.*, in the absence of amplicon), that probe is intentionally unlabeled to be compatible with the two-photon excitation and fluorescent detection system that is essential for performing the disclosed homogeneous assay. As well, neither **Mueller** not **Majlessi** discloses immobilized labeled probe prior to contact with a nucleotide polymerizing enzyme, and so that aspect of the claimed invention is missing from the cited prior art.

According to M.P.E.P. § 2143.03, "[t]o establish *prima facie* obviousness of a claimed

invention, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). In the instant case, the cited prior art does not teach or suggest the immobilized probe limitation of independent Claim 44. It follows that obviousness of the invention defined by Claim 44, and by Claims 45-48 and 50-52 which depend directly or ultimately from Claim 44, has not been established. For this additional reason, withdrawal of the § 103 rejection of these claims is appropriate.

II. The Rejection of Claim 49 Under § 103(a)

Claim 49 has been rejected under 35 U.S.C. § 103(a) over the combined disclosure of **Adams**, **Hanninen**, and **Mueller**, further in view of *J. Am. Chem. Soc.* **121**:2921-2922 (1999) ("**Fang**" hereafter). The reasoned logic of the rejection has been made of record, but essentially alleges the obviousness of modifying the construct of **Adams** to create a device for synthesizing freely diffusible RNA amplicons, and then detecting those amplicons using an immobilized molecular beacon hybridization probe in accordance with the teaching of **Fang**. Applicant respectfully traverses the rejection for the following reasons.

Consistent with the reasoning expressed above, the invention defined by instant Claim 49 cannot be considered *prima facie* obvious under § 103(a) because the suggested modification would inappropriately render the prior art unsatisfactory for its intended purpose (*see* M.P.E.P. § 2143.01). By virtue of its dependency on amended Claim 44, instant Claim 49 regards a device comprising a labeled hybridization probe having 2'-methoxy nucleotide analogs, a fluorophore moiety, and a quencher moiety. In accordance with the disclosure of **Majlessi**, and as confirmed in the Office Action (*see* first paragraph on page 8), the claimed 2'-methoxy probe is particularly adapted for capture and detection of RNA amplicons. **Fang** instructs an immobilized molecular beacon hybridization probe for capturing nucleic acid molecules (*i.e.*, DNA) from solution phase and then

reporting the hybridization using fluorescent output (*see* first sentence of col. 1 on page 2921; Figure 1; last paragraph of col. 1 on page 2922). The immobilized DNA molecules on the plate can be regenerated after hybridization, thereby making the plate reusable multiple times for DNA detection and interaction studies (*see* second full paragraph of col. 2 on page 2922). Since the primary prior art reference discloses devices that synthesize and maintain amplicons permanently attached to a solid support for the purpose of avoiding cross contamination of samples, and since the suggested obvious device based on the combination of **Adams**, **Hanninen**, **Mueller** and **Fang** operates in the production of RNA amplicons free in solution (*i.e.*, not permanently attached to the solid support, and therefore unable to suppress the cross contamination addressed by **Adams**), the modification required to create the suggested obvious device renders the primary prior art reference unsatisfactory for its intended purpose. The claimed requirement for a 2'-methoxy probe which is adapted for hybridization and detection of RNA targets highlights nonobviousness of the claimed invention. Indeed, amplicons free in solution are what **Adams** seeks to avoid.

As articulated under M.P.E.P. § 2143.01, "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *In re Gordon*, 733 F.2d 900,221 USPQ 1125 (Fed. Cir. 1984). In the instant case, the intended purpose of the device taught by the primary reference (**Adams**) is avoidance of amplicons free in solution (*i.e.*, amplicons not permanently attached to a solid support) because such amplicons are sources of carryover contamination (*i.e.*, amplicon from one reaction contaminating a target-negative sample). **Mueller** discloses the use of paired sets of primers for performing 3SR isothermal amplification reactions that produce RNA copies of a DNA sequence positioned downstream of a T7 promoter. Because RNA amplicons produced in the transcription-based 3SR reaction would be free in solution (*i.e.*, not synthesized as an extension product of an immobilized primer), any proposed modification that involves combining **Adams** and **Mueller**, not withstanding additional modifications based on the disclosures of **Hanninen** and **Fang**, would render

the device of the primary prior art reference unsatisfactory for its intended purpose. Accordingly, there can be no suggestion or motivation to make the proposed modification, and so withdrawal of the rejection of Claim 49 under § 103(a) is respectfully requested.

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the telephone number shown below.

DEPOSIT ACCOUNT INFORMATION

Please charge any fees due in connection with this submission, including the fees due under 37 C.F.R. § 1.17 for filing an RCE, to Deposit Account No. 07-0835 in the name of Gen-Probe Incorporated.

Respectfully submitted,

GEN-PROBE INCORPORATED

Dated: August 25, 2008

By: /Michael J. Gilly/

Michael J. Gilly, Ph.D.
Registration No. 42,579
Gen-Probe Incorporated
10210 Genetic Center Drive
San Diego, CA 92121
(858) 410-8657

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